Sleep Medicine Reviews 18 (2014) 393–397

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Influence of asthma on sleep disordered breathing in children: A systematic review

Pablo E. Brockmann*, Pablo Bertrand, Jose A. Castro-Rodriguez

Department of Pediatrics, School of Medicine, Pontificia Universidad Catolica de Chile, Chile

ARTICLE INFO

Article history:
Received 26 November 2013
Received in revised form
28 January 2014
Accepted 29 January 2014
Available online 7 February 2014

Keywords:
Apnea
Sleep
Snoring
Wheezing
Children

SUMMARY

The objective of this study was to perform a systematic review for the association between asthma and sleep disordered breathing (SDB) in children. We performed an electronic search in Medline, Embase, CINAHL, LILACS and Cochrane databases. Study selection criteria: children <18 y of age with diagnosis of asthma and SDB. Primary outcomes: odds ratios (OR) and 95% confidence intervals [95%CI] of asthma for SDB were calculated. There were $n = 968$ citations identified, of them $n = 17$ studies were selected, which included $n = 45\,155$ (53% males) children. All included studies defined asthma and SDB based on questionnaires, and only two performed a sleep study for diagnosing obstructive sleep apnea. Mean age was 8.6 ± 2.5 y. SDB was significantly more frequent in children with asthma compared with non-asthmatics: 23.9% vs 16.7% respectively, $p < 0.0001$. Children with asthma had a significantly higher risk for SDB: OR 1.9 [1.7; 2.2]. This systematic review showed evidence of a significant association between asthma and SDB in children. Asthma seems to be a significant risk factor for developing SDB. However, the minority of the studies based the diagnosis of SDB on polysomnography, considered the current gold standard for SDB. The physiological and temporal relationships between both conditions should be addressed in future cohort studies.

Introduction

Asthma is among the most prevalent chronic diseases in children [1]. The prevalence of asthma has rapidly increased worldwide over the last decades [2]. Similarly to the increase of the prevalence of asthma, snoring and sleep disordered breathing (SDB) have also increased reaching similar prevalence than asthma [3].

On the other hand, upper and lower airway inflammation is related to allergic diseases like rhinitis and asthma, and the release of inflammatory molecules [4]. Among these inflammatory mediators, cystenil leukotrienes have been identified in asthma [5] and also SDB [6]. Furthermore, the presence of cystenil leukotrienes seems to play an important role in the development of adenotonsillar hyperplasia that is one of the leading factors for developing SDB [7].

This similar increase in prevalence and the fact that both are diseases that are associated with a common inflammation of the airway [8], have led to the search of an association between asthma and SDB [9]. Although there have been attempts to demonstrate an association between asthma and SDB in children, there has been no state of the art systematic review to support this potential association. Therefore, we performed the present systematic review in order to analyze all available evidence for an association between asthma and SDB in children.

Methods

Search and selection criteria

We developed individual search strategies for each of the following bibliographic databases: Medline (1950–present), Embase (1988–present), CINAHL (1982–present), and LILACS (1986–present). The strategy used several combinations of searches concerning following keywords: asthma OR wheezing AND sleep apnea OR snoring OR sleep disordered breathing. We applied also individual limits for detecting only studies on subjects

Abbreviations: OR, odd's ratio; SDB, sleep disordered breathing; SD, standard deviation; ISAAC, international study on asthma and allergies in childhood; PEF, peak expiratory flow; PSQ, pediatric sleep questionnaire; RSV, respiratory syncytial virus.

* Corresponding author. Lira 85, 5to Piso, 8330074 Santiago, Chile.
E-mail address: pbrockmann@med.puc.cl (P.E. Brockmann).

http://dx.doi.org/10.1016/j.smrv.2014.01.005
1087-0792/

younger than 18 y, without language restriction. All references were managed by reference manager software (Review Manager 5.1.2, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). All database searches were started in January 2012, with an update in September 2013. Reference lists from eligible studies and review articles were crosschecked to identify additional studies. The detailed search strategy is available from the authors.

Study selection

Types of studies

All types of studies that aimed to establish an association between asthma and SDB in children were considered.

Participants

Studies including children <18 y of age were eligible for inclusion. Studies that included more than 20% of subjects with any other chronic underlying diseases (i.e., genetic/metabolic disorders, craniofacial malformations, or neurological/neuromuscular disorders) were excluded.

Target conditions

We accepted studies that clinically defined asthma as a recurrent, chronic condition, characterized by intermittent or persistent wheezing. Questionnaire based (e.g., International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire [1,10]) diagnosis of asthma was also accepted. SDB was defined according to the International Classification of Sleep Disorders 2nd edition [11], and accepted all forms of SDB (i.e., habitual snoring, upper airway resistance syndrome, and obstructive sleep apnea) as target diagnoses. The diagnosis of SDB was accepted when based on questionnaire, clinical examination, or polysomnography.

The primary outcome of the present study was the frequency of asthmatic subjects with SDB. Secondary measures were the odd's ratios (OR) and their 95% confidence intervals [95%CI] for SDB based on the diagnosis of asthma. A differentiated evaluation of those studies that objectively assessed asthma and SDB diagnosis on spirometry and polysomnography, respectively, was planned.

Data extraction

This systematic review was performed according to criteria established by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [12] and the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [13]. Titles and abstracts of records retrieved by the electronic searches were independently screened by three reviewers with experience in pediatric sleep medicine and asthma (PEB, PB, JAC). After obtaining the full text of potentially relevant articles eligibility was discussed. Disagreement between reviewers was resolved by group discussion.

Heterogeneity of the studies was assessed by the I^2 test (<40% was accepted as not relevant). Risk of bias was also investigated by the observation of Funnel plots. Quality of the included studies was assessed with the Newcastle–Ottawa scale (NOS) for assessing the quality of nonrandomised studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

Extracted data were managed with appropriate software (Review Manager 5.1.2, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and frequencies, ORs of SDB were calculated. Forest plots were constructed for the association between asthma and SDB. Descriptive statistics (mean, standard deviation [SD], median, minimum, maximum) were used to summarize studies' characteristics, and results. Comparisons of frequencies and ORs of SDB in children with asthma compared with controls were conducted with the non-parametric Mann–Whitney-*U* test.

Results

From $n = 968$ citations identified, $n = 17$ studies [8,14–29] fulfilled the inclusion criteria and were selected after discussion (Fig. 1). Selected studies included $n = 45\,155$ (53% males) children, the mean (SD) age was 8.6 (2.5). Six studies were conducted in Asia [15,18,19,29–31], five in Europe [8,16,17,23,27], four in the US [20,22,25,26], and two in Australia [24,28]. Almost all studies assessed asthma and SDB based on questionnaires or clinical history, there was only one study that performed polysomnography [25] and one a home cardiorespiratory polygraphy [26]. The ISAAC questionnaire was specifically used in five studies [17,22,28–30], the remaining used similar items or unstructured questionnaires for assessing asthma. Spirometry was performed only in four studies [17,20,22,26]. Details on the description of the included studies are given in Table 1. Sensitivity analysis between age groups (like pre-schoolers, school aged children or adolescents) or gender was not possible, as no study provided differentiated results analysis concerning the association between asthma and SDB.

Eight of the included studies [14,16,18,19,21,24,25,32] intended to investigate the prevalence of SDB, and asthma was assessed among other studied risk factors. In contrast, there were $n = 8$ studies [8,15,17,22,23,26,28,29] that investigated risk factors for asthma. One study analyzed nocturnal symptoms of asthma [20], among which data on snoring were extractable.

Median (minimum–maximum) SDB prevalence was 23.9% (7.1%–77.3%) in children with asthma compared to 16.7 (5.1–69.5)% in those without (p-value <0.0001). Details on the frequencies are given in Table 1.

Quality assessment

Quality assessment is shown in Fig. 2. Median obtained NOS score was 5/10. Lowest scores were obtained in the question concerning the ascertainment of exposure (see Fig. 2), only one study obtained data based on secure records or structured interviews. All other studies obtained data based on parental questionnaires or

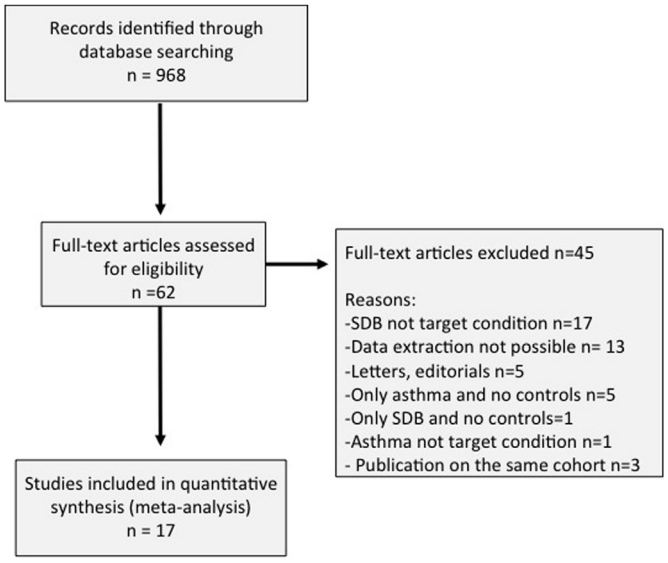

Fig. 1. Study selection process.

Table 1
Included original publications.

Author & year	Country	*n*	Male	Mean age (years)	Asthma diagnosis	SDB diagnosis	SDB prevalence (%) Asthma vs controls
Bidad 2006 [14]	Iran	2900	1200	14	ISAAC questions	Snoring for ≥3 nights/wk	10.7 vs 7.1
Chng 2004 [15]	Singapore	11 114	5212	5.8	Asthma in questionnaire	Snoring for >3 nights/wk	8.6 vs 5.1
Corbo 2001 [16]	Italy	2209	722	12.5	Physician diagnosed asthma or questionnaire	Snoring "often"	12.2 vs 7.6
Desager 2005 [17]	Belgium	1234	Not given	9.6	ISAAC questionnaire Spirometry	Snoring	31.4 vs 20.7
Ersu 2004 [18]	Turkey	2147	1074	8.5	History of asthma, questionnaire	"Often" or "always" snoring	9.1 vs 7.6
Fadzil 2012 [19]	Malaysia	550	285	8.5	Asthma in questionnaire	PSQ >0.33	29.2 vs 13.5
Hoskyns 1995 [20]	UK	33	19	9.5	Asthma diary and PEF meter	"Persistent" snorers	27.6 vs 14.3
Kaditis 2010 [8]	Greece	442	241	7.6	Physician-diagnosed wheezing treated with corticosteroids	"Habitual" snoring	26.1 vs 18.3
Li 2010 [21]	China	20 152	9890	9.0	Asthma ever diagnosed	"Frequently" or "almost always" snoring	17.8 vs 10.5
Lu 2003 [24]	Australia	974	516	Not given (2–5)	Asthma in questionnaire	Snoring for ≥4 nights/wk	15.8 vs 8.4
Marshall 2007 [22]	US	219	107	5.0	ISAAC questionnaire Spirometry	Snoring for >3 nights/wk	29.1 vs 16.9
Pescatore 2014 [23]	UK	1226	678	5.0	Current wheeze plus use of asthma medication in the last 12 mo	Sometimes without colds/almost always	77.3 vs 69.5
Ramagopal 2008 [25]	US	236	147	7.2	History of asthma or asthma related medication used	Polysomnography, AHI >2	28.9 vs 29.3
Sulit 2005 [26]	US	788	393	9.5	Wheezing reported by parents or use of medications, Spirometry	Portable polygraphy, AHI >5	21.4 vs 13.3
Urschitz 2004 [27]	Germany	1144	585	9.6	History of asthma	"Frequently" or "always" snoring	7.1 vs 9.8
Valery 2004 [28]	Australia	1650	Not given	8.5	ISAAC questionnaire	Snoring	17.4 vs 9.7
Verhulst 2007 [29]	Sri Lanka	652	432	8.4	ISAAC questionnaire	Snoring	36.4 vs 22.2

AHI: apnea-hypopnea index; ISAAC: international study on asthma and allergies in childhood; SDB: sleep disordered breathing.
PEF, peak expiratory flow; PSQ, pediatric sleep questionnaire.

self-reports. There was only one study that obtained all possible points in the NOS quality scale.

Asthma as a risk factor for SDB

In $n = 15$ studies there was a higher OR for SDB in children with asthma. Overall [95%CI] OR for developing SDB when asthma was present was 1.9 [1.7–2.2]. Fig. 3 gives details on ORs [95%CIs] and the Forest plot for all included studies. In the two studies [25,26] that objectively assessed SDB the overall OR [95%CI] was 1.49 [1.04–2.13], see Fig. 4.

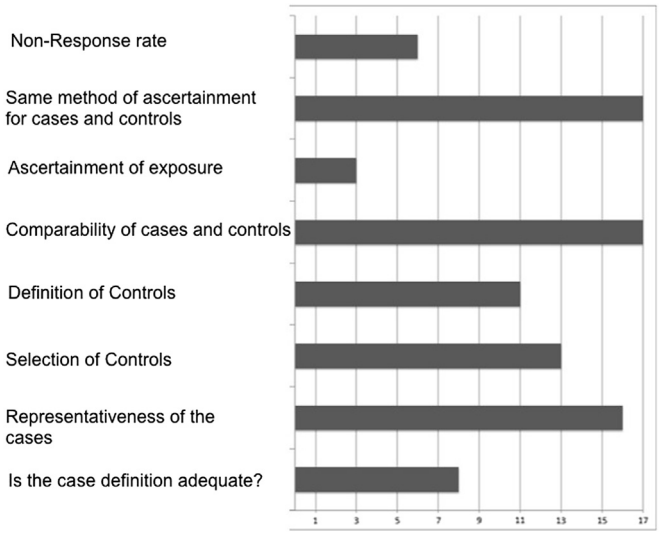

Fig. 2. Quality of the included studies. *X*-axis shows the score, *Y*-axis shows the items of the NOS scale.

Discussion

To our knowledge this is the first systematic review performed exclusively among children that explored the present evidence for supporting an association between asthma and SDB.

Our study demonstrated that asthma was significantly associated with the development of SDB. Children with asthma showed almost two times the chance for having SDB than those without asthma. These results are consistent with the solid evidence supporting an association of asthma and SDB in adults [9,33]. These results are interesting as they demonstrate for the first time in a meta-analysis that there is an association between both diseases. Interestingly, most studies based their definition of asthma on questionnaires or information obtained via an unstructured interview. The most frequently used tool for assessing asthma was the ISAAC questionnaire [10]. The use of such an internationally validated and widely used questionnaire seems to be reasonable and gives certain homogeneity to the diagnosis of asthma in this population. SDB was investigated in almost all studies with questionnaires. The most commonly used definition for SDB was based on habitual snoring (i.e., snoring >3 nights a weeks), and not on polysomnography. In fact, only two studies performed any type of sleep studies in the included children [25,26]. As the current reference standard for diagnosing obstructive sleep apnea is polysomnography, it is not possible to postulate of an association between asthma and obstructive sleep apnea. Ramagopal et al. published in 2008 their study on 236 children and performed a state-of-the-art polysomnography in all of the recruited subjects [25]. In that study, the presence of asthma was no significant risk for obstructive sleep apnea based on polysomnography [25]. So far, Ramagopal et al.'s publication has been the only included study that performed a state-of-the-art polysomnography. This fact reflects the variety and importance of definitions that were used in the included studies. The lack of the currently accepted gold

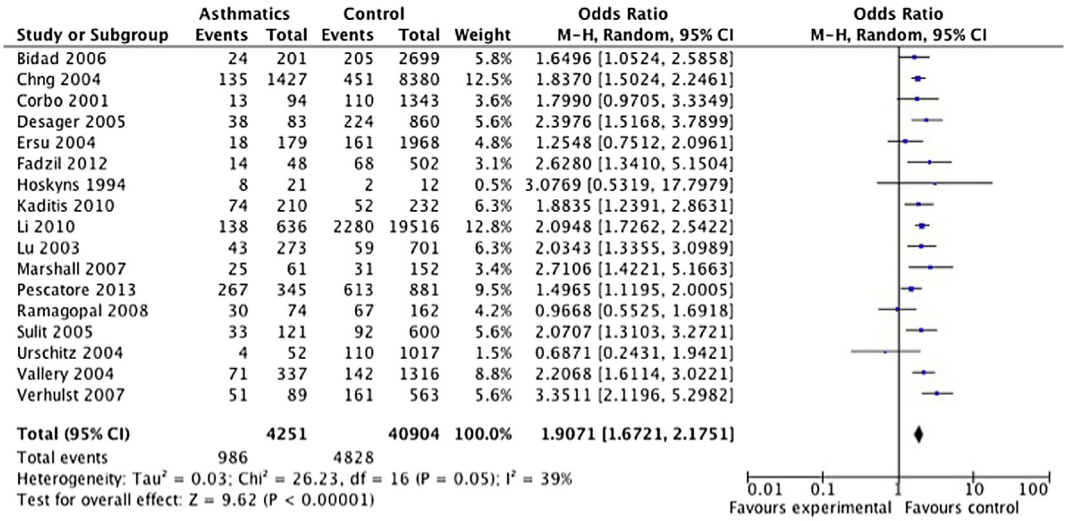

Fig. 3. Forest plot of the association between asthma and SDB.

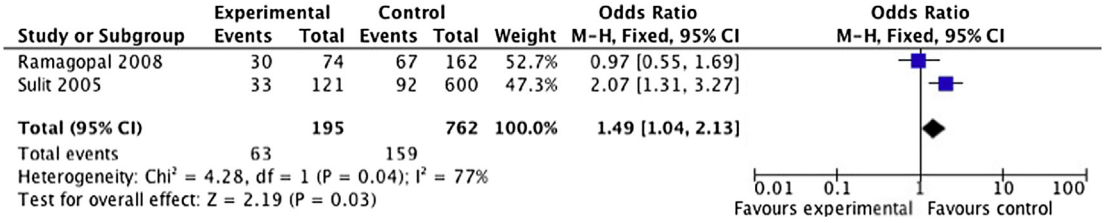

Fig. 4. Forest plot of the association between asthma and obstructive sleep apnea measured by a sleep study.

standard (i.e., polysomnography) in most of studies makes it impossible to assume any increased risk for obstructive sleep apnea in children with asthma. However, there is demonstration of an association between asthma and SDB measured by questionnaires. We hypothesize that milder forms of SDB like primary snoring or the upper airway resistance syndrome may be more associated with asthma. There was only one study that analyzed if asthma was associated with severity of SDB [25]. However, that study compared children with or without obstructive sleep apnea based on different cutoffs of the apnea hypopnea index. So far, there has been no study that investigated if asthma is associated with milder forms of SDB.

On the other hand, none of the included studies analyzed the relationship between the severity of asthma and the presence of SDB. The definition of asthma severity in children may be difficult, but there are guidelines that would help to assess it. This lack of a consistent definition was probably caused by the lack of an ascertainment of the exposure (i.e., the presence of asthma and SDB). Most studies performed questionnaires that were given to the parents and only two performed a structured interview or based their data on secure records. Self-report is surely a widely used research tool. However, there is still a lack of a study that investigates asthma severity based on a structured interview, physical examination, and lung function. We encourage the objective assessing of SDB and asthma in future studies on this topic.

The association between asthma and SDB seems to be evident from a physiological point of view. A common inflammatory pathway of the airway may link asthma and SDB. It has been also demonstrated that lung samples of children infected with respiratory syncytial virus (RSV) and adenotonsils extracted from children with obstructive sleep apnea have similar pathological changes [34]. This fact is especially interesting, as RSV has been associated to the development of asthma [35–38] and also SDB [39]. Furthermore, even RSV associated neuro-immunomodulatory changes have been postulated as common mechanism for asthma and SDB [40].

As all meta-analyses, there might have been potential classification error, which may be increased due to the diverse asthma definitions accepted in the present study. Also, we accepted broad range of SDB definitions. This was intended in order to obtain as much information as possible. A diagnostic restriction seemed not to be ideal at this point. Now that there is consistent evidence to support an association between asthma and SDB, studies with objectively defined diagnoses are surely needed. Another limitation of the study was that, the inherent limitations of each selected study are incorporated. There were many studies in which proper data extraction was not possible and had to be discarded. In the finally included study, assessing an association between asthma and SDB was often not the primary objective. Hence, this might have also biased the results. The lack of information stratified by age, gender, use of medications, and race is also a limitation. This fact reflects the need for a standardized form of data presentation that helps readers and reviewers to analyze data.

Conclusions

The present systematic review demonstrates that asthma is significantly associated with SDB. However, there are few studies in which asthma and SDB was objectively assessed. How asthma leads to developing SDB later in life is still unknown. Physiological and temporal relationships between both conditions should be investigated in future cohort studies.

Practice points

- There seems to be an association between asthma and sleep disordered breathing in children.
- Children with asthma have two times the more sleep disordered breathing than those without asthma.

Research agenda

- There is a need for studies that perform polysomnography for diagnosing obstructive sleep apnea in children with asthma.
- The physiological pathways that explain the association between asthma and sleep disordered breathing should be investigated.
- There is a need of cohort studies that follow-up children with asthma and sleep disordered breathing.

Disclosures

The authors have no financial disclosures or conflicts of interest to declare.

Acknowledgments

This study was supported by the Department of Pediatrics, School of Medicine, Pontificia Universidad Catolica de Chile and received no other/external financial support.

We would like to thank Mr. Richard F. Dewhirst for his help with editing the manuscript.

References

*[1] Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: a global synthesis. Allergol Immunopathol (Madr) 2013;41:73–85.
[2] Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2007;62:758–66.
*[3] Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc 2008;5:242–52.
[4] Bisgaard H. Role of leukotrienes in asthma pathophysiology. Pediatr Pulmonol 2000;30:166–76.
[5] Brockmann PE, Castro-Rodriguez JA, Holmgren NL, Cerda J, Maria Contreras A, Moya A, et al. Urinary leukotriene excretion profile in children with exercise-induced asthma compared with controls: a preliminary study. Allergol Immunopathol (Madr) 2012;40:181–6.
[6] Goldbart AD, Goldman JL, Veling MC, Gozal D. Leukotriene modifier therapy for mild sleep-disordered breathing in children. Am J Respir Crit Care Med 2005;172:364–70.
*[7] Goldbart AD, Goldman JL, Li RC, Brittian KR, Tauman R, Gozal D. Differential expression of cysteinyl leukotriene receptors 1 and 2 in tonsils of children with obstructive sleep apnea syndrome or recurrent infection. Chest 2004;126:13–8.
*[8] Kaditis AG, Kalampouka E, Hatzinikolaou S, Lianou L, Papaefthimiou M, Gartagani-Panagiotopoulou P, et al. Associations of tonsillar hypertrophy and snoring with history of wheezing in childhood. Pediatr Pulmonol 2010;45:275–80.
*[9] Teodorescu M, Consens FB, Bria WF, Coffey MJ, McMorris MS, Weatherwax KJ, et al. Predictors of habitual snoring and obstructive sleep apnea risk in patients with asthma. Chest 2009;135:1125–32.
[10] Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. Lancet 2006;368:733–43.
[11] American Academy of Sleep Medicine, editor. International classification of sleep disorders. 2nd ed. 2005.
[12] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[13] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. J Am Med Assoc 2000;283:2008–12.
[14] Bidad K, Anari S, Aghamohamadi A, Gholami N, Zadhush S, Moaieri H. Prevalence and correlates of snoring in adolescents. Iran J Allergy Asthma Immunol 2006;5:127–32.
[15] Chng SY, Goh DY, Wang XS, Tan TN, Ong NB. Snoring and atopic disease: a strong association. Pediatr Pulmonol 2004;38:210–6.
[16] Corbo GM, Forastiere F, Agabiti N, Pistelli R, Dell'Orco V, Perucci CA, et al. Snoring in 9- to 15-year-old children: risk factors and clinical relevance. Pediatrics 2001;108:1149–54.
[17] Desager KN, Nelen V, Weyler JJ, De Backer WA. Sleep disturbance and daytime symptoms in wheezing school-aged children. J Sleep Res 2005;14:77–82.
[18] Ersu R, Arman AR, Save D, Karadag B, Karakoc F, Berkem M, et al. Prevalence of snoring and symptoms of sleep-disordered breathing in primary school children in Istanbul. Chest 2004;126:19–24.
[19] Fadzil Abdullah AA, Jamalludin AR, Norrashidah AW, Norzila MZ, Asiah Kassim K, Rus Anida A, et al. Prevalence of sleep disordered breathing symptoms among Malay school children in a primary school in Malaysia. Med J Malaysia 2012;67:181–5.
[20] Hoskyns EW, Beardsmore CS, Simpson H. Chronic night cough and asthma severity in children with stable asthma. Eur J Pediatr 1995;154:320–5.
*[21] Li S, Jin X, Yan C, Wu S, Jiang F, Shen X. Habitual snoring in school-aged children: environmental and biological predictors. Respir Res;11:144.
[22] Marshall NS, Almqvist C, Grunstein RR, Marks GB, Childhood Asthma Prevention S. Predictors for snoring in children with rhinitis at age 5. Pediatr Pulmonol 2007;42:584–91.
[23] Pescatore AM, Dogaru CM, Duembgen L, Silverman M, Gaillard EA, Spycher BD, et al. A simple asthma prediction tool for preschool children with wheeze or cough. J Allergy Clin Immunol 2014;133:111–8.
[24] Lu LR, Peat JK, Sullivan CE. Snoring in preschool children: prevalence and association with nocturnal cough and asthma. Chest 2003;124:587–93.
*[25] Ramagopal M, Scharf SM, Roberts DW, Blaisdell CJ. Obstructive sleep apnea and history of asthma in snoring children. Sleep Breath 2008;12:381–92.
*[26] Sulit LG, Storfer-Isser A, Rosen CL, Kirchner HL, Redline S. Associations of obesity, sleep-disordered breathing, and wheezing in children. Am J Respir Crit Care Med 2005;171:659–64.
[27] Urschitz MS, Guenther A, Eitner S, Urschitz-Duprat PM, Schlaud M, Ipsiroglu OS, et al. Risk factors and natural history of habitual snoring. Chest 2004;126:790–800.
[28] Valery PC, Masters IB, Chang AB. Snoring and its association with asthma in Indigenous children living in the Torres Strait and Northern Peninsula Area. J Paediatr Child Health 2004;40:461–5.
[29] Verhulst SL, Vekemans K, Ho E, Aerts L, Jacobs S, De Backer LA, et al. Is wheezing associated with decreased sleep quality in Sri Lankan children? A questionnaire study. Pediatr Pulmonol 2007;42:579–83.
[30] Bidad K, Anari S, Aghamohammadi A, Pourpak Z, Moayeri H. Prevalence of asthma related to BMI in adolescents in Tehran, Iran, 2004–2005. Eur J Pediatr 2007;166:453–4.
[31] Arens R, McDonough JM, Corbin AM, Rubin NK, Carroll ME, Pack AI, et al. Upper airway size analysis by magnetic resonance imaging of children with obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2003;167:65–70.
[32] Urschitz MS, Eitner S, Guenther A, Eggebrecht E, Wolff J, Urschitz-Duprat PM, et al. Habitual snoring, intermittent hypoxia, and impaired behavior in primary school children. Pediatrics 2004;114:1041–8.
*[33] Teodorescu M, Polomis DA, Teodorescu MC, Gangnon RE, Peterson AG, Consens FB, et al. Association of obstructive sleep apnea risk or diagnosis with daytime asthma in adults. J Asthma 2012;49:620–8.
[34] Salerno FG, Carpagnano E, Guido P, Bonsignore MR, Roberti A, Aliani M, et al. Airway inflammation in patients affected by obstructive sleep apnea syndrome. Respir Med 2004;98:25–8.
[35] Li QG, Wu XR, Li XZ, Yu J, Xia Y, Wang AP, et al. Neural-endocrine mechanisms of respiratory syncytial virus-associated asthma in a rat model. Genet Mol Res 2012;11:2780–9.
[36] Martinez FD. Respiratory syncytial virus bronchiolitis and the pathogenesis of childhood asthma. Pediatr Infect Dis J 2003;22:S76–82.
[37] Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. Thorax 2010;65:1045–52.
[38] Piedimonte G. Respiratory syncytial virus and asthma: speed-dating or long-term relationship? Curr Opin Pediatr 2013;25:344–9.
*[39] Snow A, Dayyat E, Montgomery-Downs HE, Kheirandish-Gozal L, Gozal D. Pediatric obstructive sleep apnea: a potential late consequence of respiratory syncitial virus bronchiolitis. Pediatr Pulmonol 2009;44:1186–91.
[40] Goldbart AD, Mager E, Veling MC, Goldman JL, Kheirandish-Gozal L, Serpero LD, et al. Neurotrophins and tonsillar hypertrophy in children with obstructive sleep apnea. Pediatr Res 2007;62:489–94.

* The most important references are denoted by an asterisk.